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Anatomy and physiology of erection and sexual response & Common causes and co-morbidities associated with erectile dysfunction

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Overview

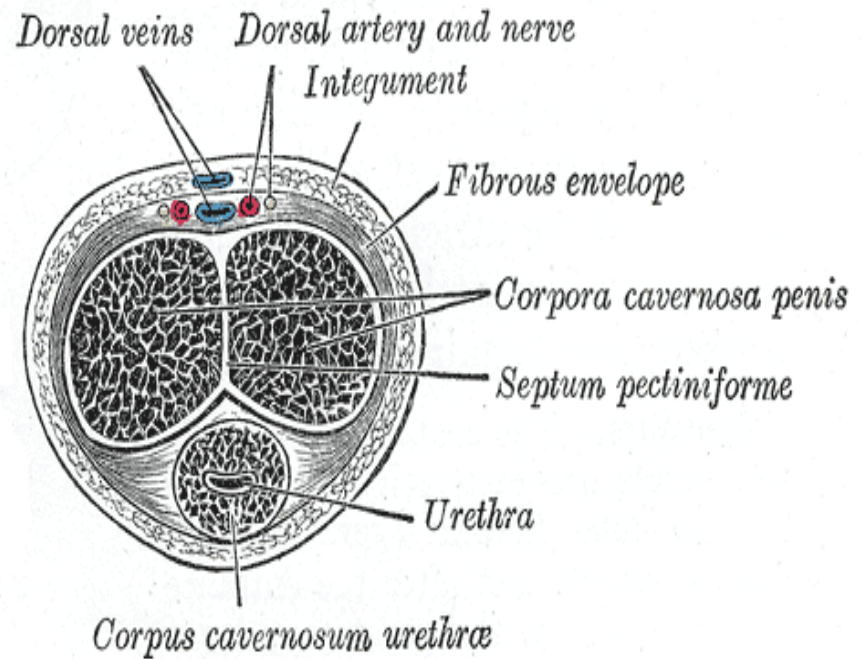
- Review of the physiological basis of normal erectile function (EF)
- Identification of how various conditions exert their effects on EF, some of which may be related to the condition, or related to treatment with various medicines
- Consider risk factors associated with development of ED

What is ED?

- ‘persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity’
- Erectile dysfunction is the inability of a man to get an erection of sufficient quality for sexual activity

The penis

- 3 cylindrical structures - paired corpora cavernosa & corpus spongiosum (which houses the urethra) - covered by a loose subcutaneous layer and skin.
- Flaccid length is controlled by the contractile state of the erectile smooth muscle (varies considerably) - depending on emotion and ambient temperature
- Neither age nor the size of the flaccid penis accurately predicts erectile length





Erection

- Release of neurotransmitters from the cavernous nerve terminals - relaxation of smooth muscles and the following events:
- Arterial & arteriole dilatation - increased blood flow into the expanding sinusoids
- Venous compression - reducing venous outflow
- Sinusoidal relaxation & stretching of the tunica to its capacity - occludes the emissary veins and further decreases the venous outflow to a minimum
- An increase in PO₂ (to about 90 mmHg) and intracavernous pressure (around 100 mm Hg), which raises the penis from the dependent position to the erect state (the full-erection phase)
- A further pressure increase (to several hundred mmHg) with contraction of the ischiocavernosus muscles (rigid-erection phase)



Psychogenic (supraspinal) erections

- Occur under the influence of activity in the cerebral cortex and neural impulses - origins can be localised to the thoracolumbar erection centre in the spinal cord (level T10 to L2).
- From there, impulses continue to travel to the penis, specifically the vascular network within the corpora cavernosa and spongiosum.
- In the absence of direct mechanical stimulation, erections of this type are generally initiated in response to visual, auditory, olfactory, tactile stimuli or imaginary stimuli.
- The cortex also has the capacity to suppress erection, even in the presence of mechanical stimulation, as can other psychological, environmental and emotional factors.



Reflex erections

- The result of tactile stimuli applied to the penis or genital area - generates a simple reflex arc with the sacral erectile centre located within the sacral spinal cord (levels S2-4; the sacral erectile centre).
- May be seen in some men following partial, or complete spinal cord injuries.
- Some studies indicate that despite spinal cord injury, men may be able to achieve erections sufficient to enable penetration, even though their injuries have resulted in a lack of control over other bodily functions (Goldstein 2000) - this, however also crucially depends upon the level of injury.



Spontaneous tumescence

- Involuntary, commonplace and a normal physiological phenomenon
- Usually occur three to four times during the night – as either nocturnal penile tumescence (NPT), or early morning tumescence (EMT)
- Tend to occur during rapid eye movement (REM) sleep, the stage in which dreaming occurs
- Coincide with reduced sympathetic nervous system activity during REM sleep (specifically the locus coeruleus in the brain stem) – when proerectile parasympathetic activity predominates
- Nutritive role - maintain regular blood-flow and oxygenation to the penis.
- Men suffering from depression, sleep disorders (including obstructive sleep apnoea), and abnormal/reduced REM phase may not experience spontaneous tumescence.
- Absence of spontaneous tumescence is also commonly used to distinguish between organic and psychological causes of erectile dysfunction.



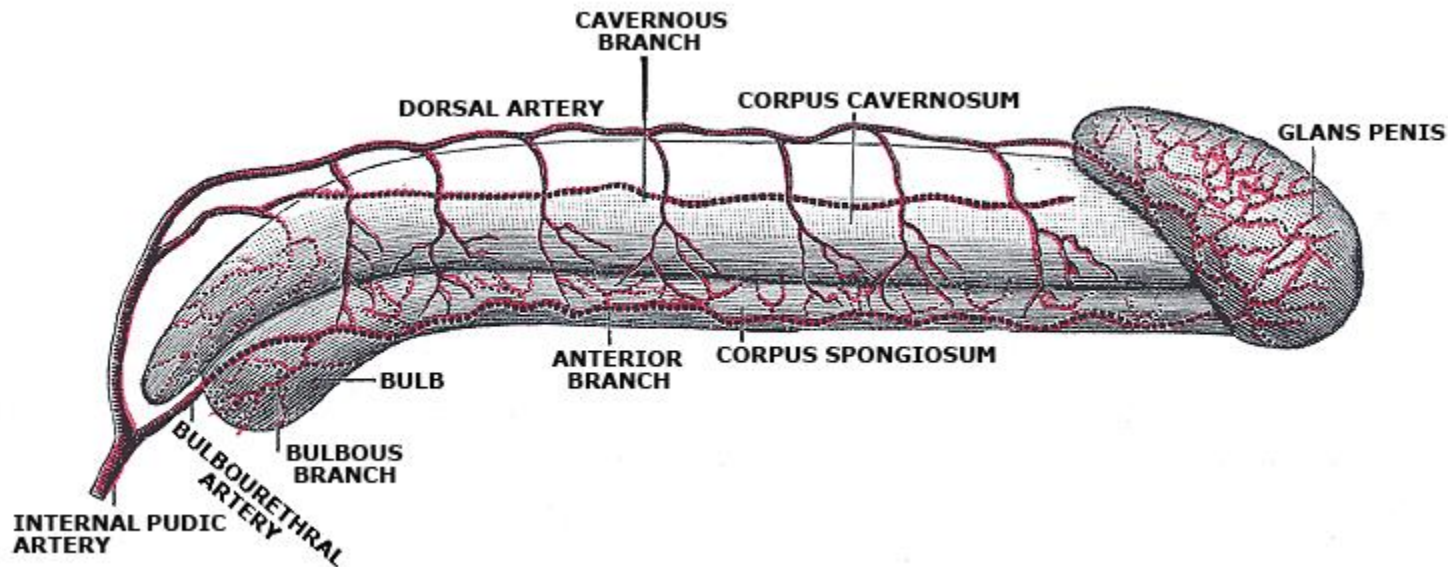
Haemodynamics of Erection

Corpora Cavernosa

- The penile erectile tissue (cavernous smooth muscle and smooth muscles of the arteriolar and arterial walls), plays a key role.
- In flaccid state - smooth muscles are tonically contracted, allowing only a small amount of arterial flow for nutritive purposes.
- Both corpora cavernosa separated by incomplete septum, which allows them to fill/ function in unison.

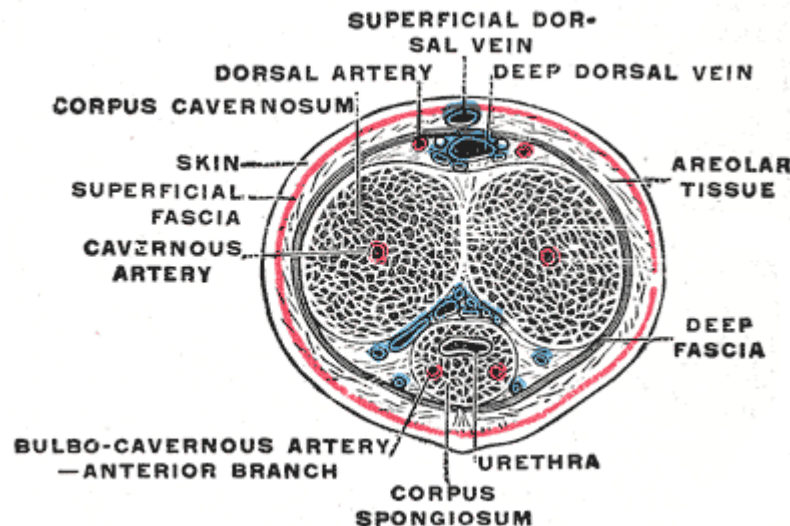
Arterial supply

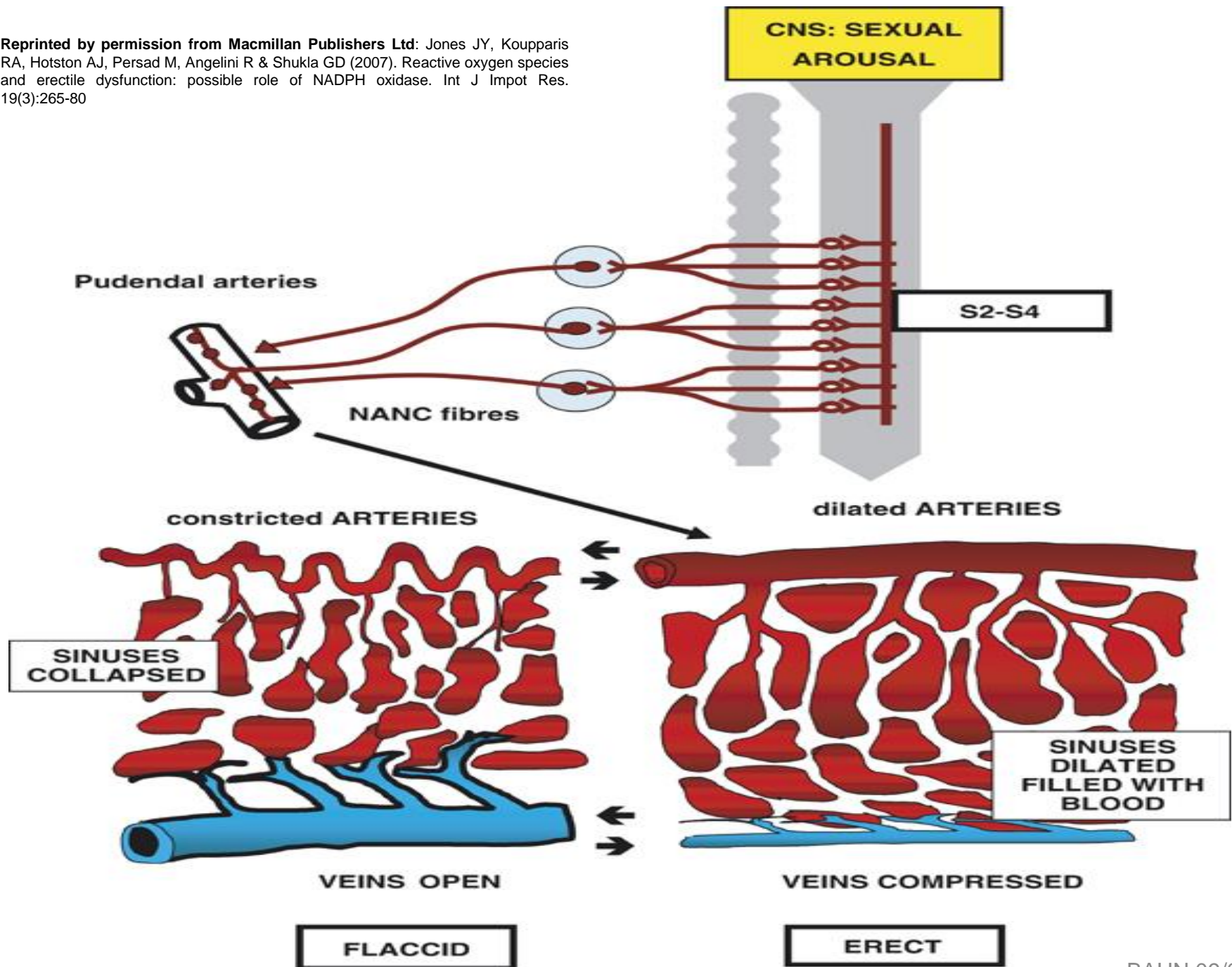
- Penile blood supply - the internal pudendal artery (off internal iliac artery) → common penile artery
- 3 branches - dorsal, cavernousul and bulborethral
- Dorsal artery is responsible for engorgement of the glans during erection



Venous supply

- Venous drainage from the three corpora originates in tiny venules leading (from sinusoids) – exit as the emissary veins







Corpus Spongiosum and Glans Penis

- Haemodynamics of the corpus spongiosum and glans different from those of the corpora cavernosa.
- During erection - arterial flow increases in a similar manner; however, the pressure in the corpus spongiosum and glans is only $\frac{1}{3}$ - $\frac{1}{2}$ of that in the corpora cavernosa because the tunical covering (virtually absent over the glans and thin over the corpus spongiosum) ensures minimal venous occlusion.



Neuroanatomy and Neurophysiology of Erection

Peripheral innervation of the penis is:

- **Autonomic**
 - Sympathetic
 - Parasympathetic
- **Somatic**
 - Sensory
 - Motor



Neural Input

- In the spinal cord and peripheral ganglia - sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa and corpus spongiosum.
- In the flaccid state, dominance of sympathetic activity keeps arterioles and smooth muscle contracted
- Erections are primarily vascular in nature BUT result from pro-erectile parasympathetic stimulation
- Causes arteriolar dilation and trabecular smooth-muscle relaxation.
- Pudendal nerve also has an input causing ischiocavernosus muscle contraction, which further increases intracavernosal pressure



Autonomic Pathways 1

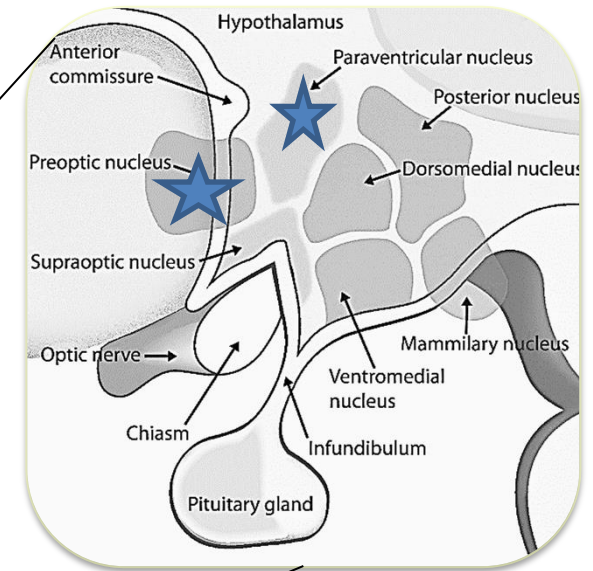
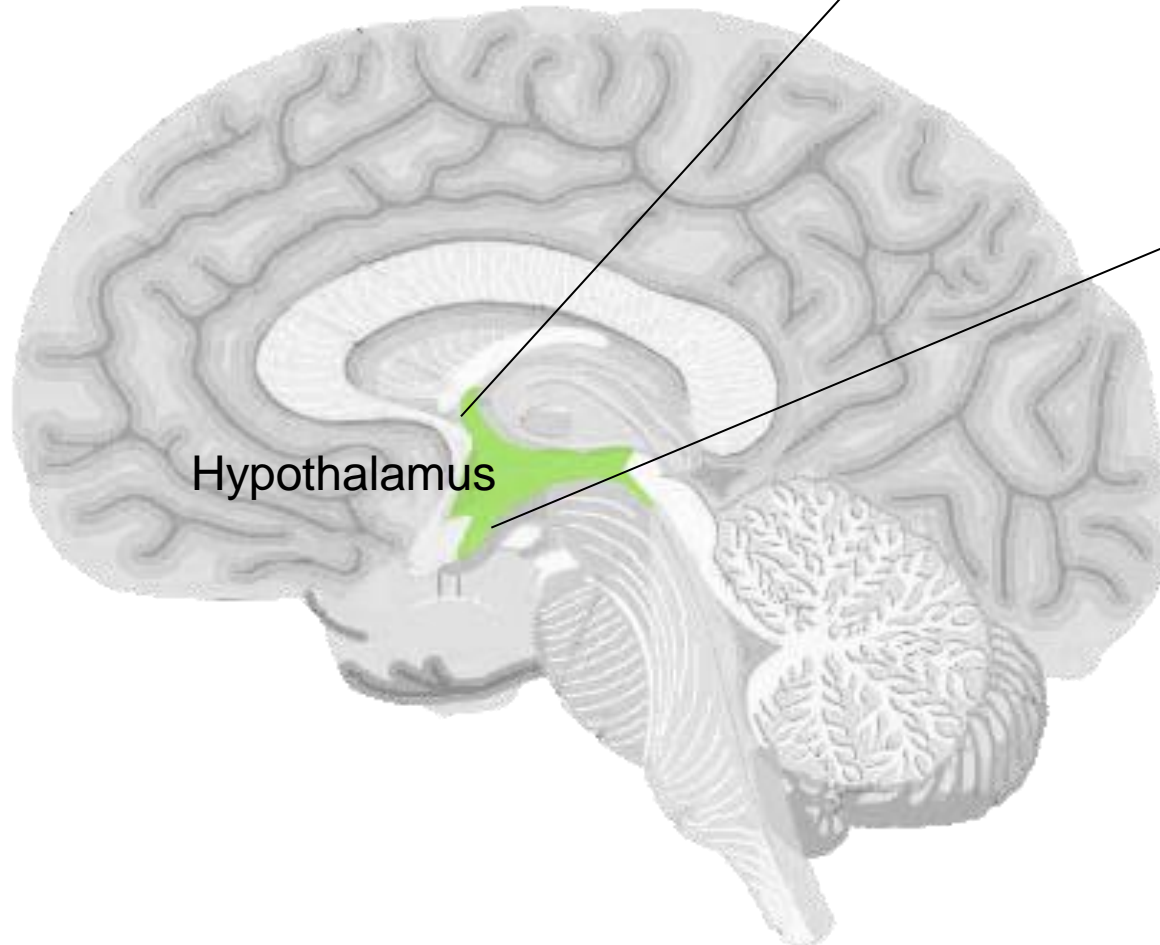
- Sympathetic pathway - originates from the T11 – L2 spinal segments
- Passes through the white rami to the sympathetic chain ganglia.
- Some fibres then travel through the lumbar splanchnic nerves to the inferior mesenteric and superior hypogastric plexuses, from which fibres travel in the hypogastric nerves to the pelvic plexus.
- In humans, T10 to T12 segments are most often the origin of sympathetic fibres projecting to the penis (sacral and caudal sympathetic chain ganglia).



Autonomic Pathways 2

- The parasympathetic pathway - arises from neurons in the intermediolateral cell columns of sacral spinal cord (S2-S4). The preganglionic fibres pass in the pelvic nerves to the pelvic plexus, where they are joined by the sympathetic nerves from the superior hypogastric plexus.
- The cavernous nerves - branches of the pelvic plexus that innervate the penis. Other branches of the pelvic plexus innervate the rectum, bladder, prostate, and sphincters.
- The cavernous nerves are easily damaged during abdominal surgery, including radical excision of the rectum, bladder, and prostate.

Central Control of Erections





Central Control of Erections

- ❖ Cerebral cortex – thinking about sex
- ❖ Limbic system - how we feel about sex, how we behave sexually
- ❖ Hypothalamus - stimulation triggers arousal > orgasm

Processing of input from the senses:

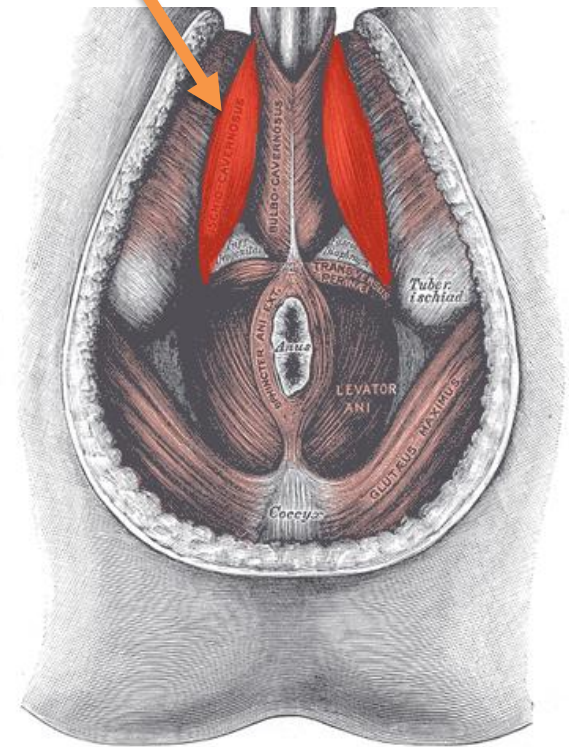
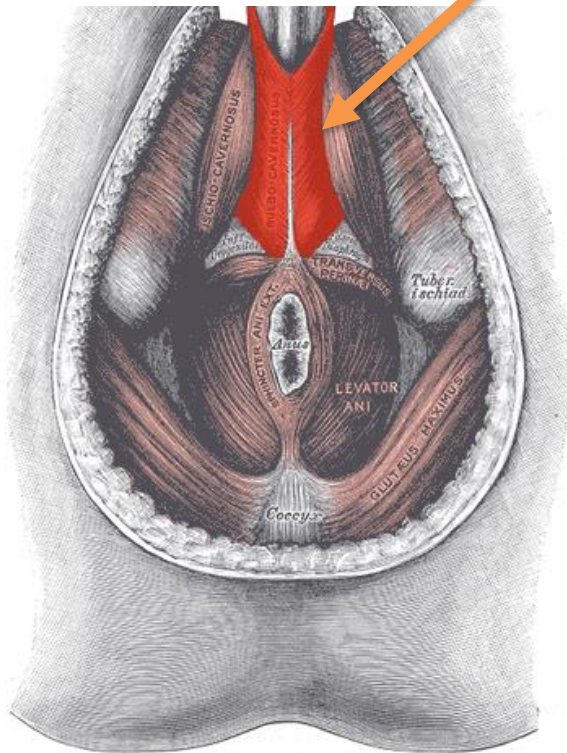
- Touch - primary & secondary erogenous zones - dominant “sexual sense”
- Vision – important role
- Smell - may cause, or attenuate arousal (? role of pheromones)
- Taste – variable role
- Hearing – variable role



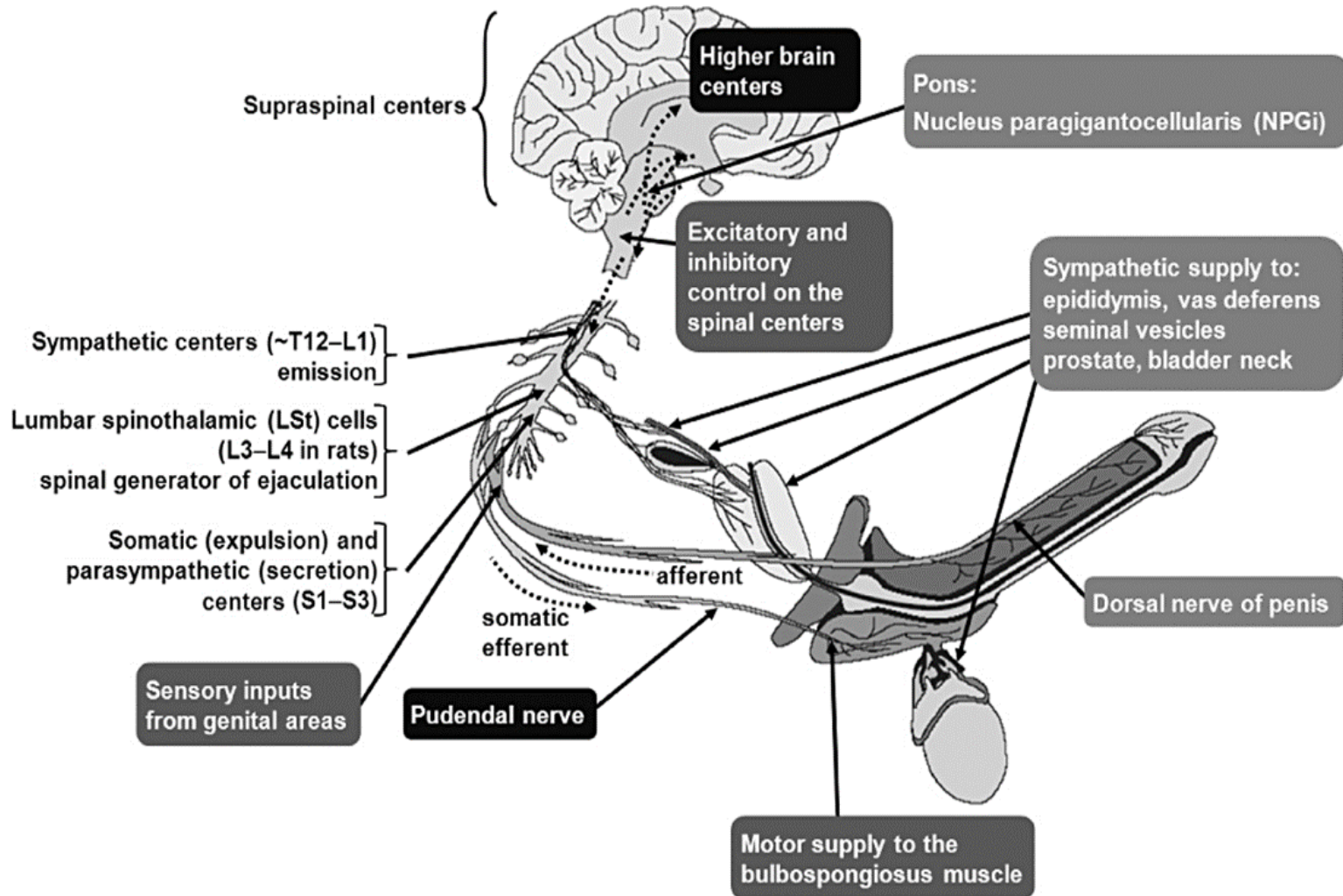
Somatic Pathways

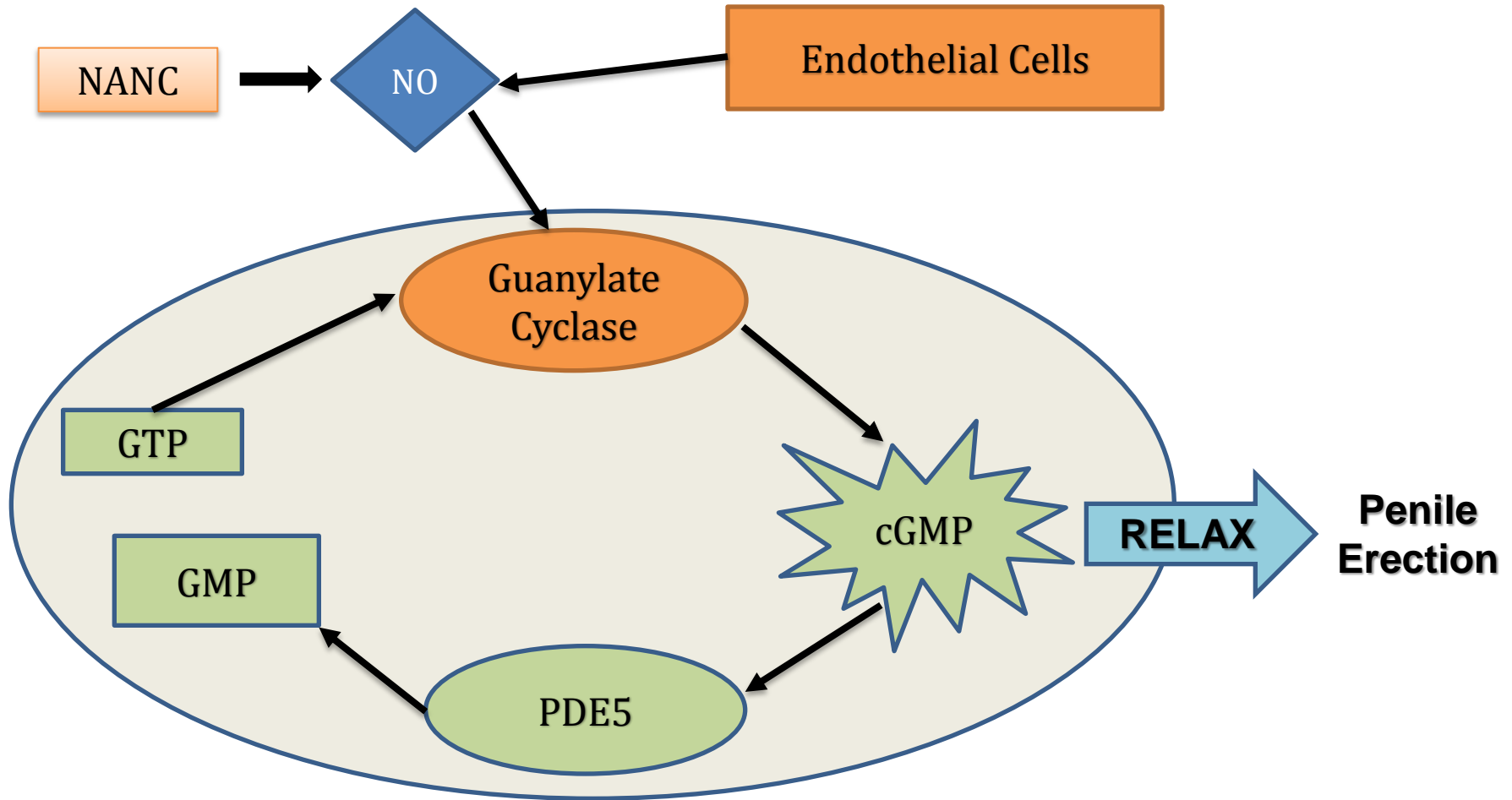
- The somatosensory pathway originates at the sensory receptors in the penile skin, glans, and urethra and within the corpus cavernosum
- The free nerve endings are derived from thin myelinated A_{δ} and unmyelinated C fibers
- Nerve fibers from the receptors converge to form bundles of the dorsal nerve of the penis, which joins other nerves to become the **pudendal nerve**
- Onuf's nucleus (S2-S4) is the center of somatomotor penile innervation
- Contraction of the ischiocavernosus muscles produces the rigid-erection phase. Rhythmic contraction of the bulbocavernosus muscle is also necessary for ejaculation.

The **somatic nerves** are primarily responsible for sensation and the contraction of the **bulbocavernosus** and **ischiocavernosus** muscles.



Neurophysiology of Erection







Summary

- Relaxation of the cavernous smooth muscle = key to penile erection.
- NO-release initiates the erection process & helps maintain erection - released from parasympathetic nerve terminals
- Parasympathetic nerve terminal also releases acetylcholine (Ach) - stimulates vascular endothelium to also release NO
- NO stimulates the production of cGMP in smooth muscle cells.
- Cyclic GMP activates protein kinase G, which causes potassium channels to open and calcium channels to close.
- Low cytosolic calcium favours smooth muscle relaxation.
- The smooth muscle regains its tone when cGMP is degraded by phosphodiesterase – this underpins the action of PDE5Is



Flaccidity and Detumescence

- Background partial contraction of intracorporeal smooth muscle influenced by three factors:
 1. Intrinsic myogenic tone
 2. Adrenergic neurotransmission
 3. Endothelium-derived contracting factors such as angiotensin II, $\text{PGF}_{2\alpha}$, and endothelins
- α -Adrenergic nerve fibres and receptors - norepinephrine = principal neurotransmitter to control penile flaccidity and detumescence
- Detumescence and return to flaccid state – also result of \downarrow NO release, the breakdown of cyclic guanosine monophosphate (cGMP) by phosphodiesterases, or sympathetic discharge during ejaculation
- Endothelin - potent vasoconstrictor produced by the endothelial cells, may be a mediator



Sexual Response Cycles

- **Kaplan**
 - Desire
 - Distinct (not required)
 - Excitement
 - Orgasm
- **Masters & Johnson**
 - Excitement Phase
Vasocongestion, myotonia, flush
 - Plateau Phase
 - Orgasm Phase
 - Resolution Phase
 - Refractory period



THE SEXUAL RESPONSE

- Masters and Johnson: four phases
- Excitation:
 - Vasocongestion: pelvic area receives more blood in general, in particular to genitals.
 - penile erection
 - scrotal sac thickens, elevates
 - sex flush (can happen later)
 - heart rate, respiration rate gradually increase
 - generalized myotonia



THE SEXUAL RESPONSE

- Plateau:
 - continued vasocongestion
 - Heart rate, respiration rate and blood pressure continue to increase
 - Perspiration
 - Increased myotonia
 - Cowper's glands secrete fluid through tip of penis
 - scrotum even higher and testicles bigger



THE SEXUAL RESPONSE

- Orgasm:
 - Males: spinal reflex triggers two phases:
 - contraction of seminal vesicles, vas and prostate (emission: fluid in urethral bulb)
 - contraction of urethra and penis: expulsion: semen expelled
 - Sensation experienced = Ejaculatory Inevitability
- Accompanied by increased heart rate, blood pressure and breathing rate
- Intense myotonia



THE SEXUAL RESPONSE

Resolution phase

- The resolution phase (Refractory period) occurs after orgasm
- Subsidence in any sex-flush and a feeling of relaxation, blood pressure drops and the body recovers from excited state
- During this time man is unable to orgasm again (refractory period)
- Associated with production of oxytocin & prolactin centrally (Exton et al., 2001).
- The duration of recovery, commonly referred to as the post-ejaculatory recovery time (PERT) and the intensity of the refractory period can be very short in younger men, whereas in mid-life and in older men, it can last for as long as a few hours, or days (Exton et al., 2001).



Psychogenic and Psychiatric causes

Two possible mechanisms have been proposed:

- ❖ Exaggeration of the normal suprasacral inhibition, leading to direct inhibition of the spinal erection centre by the brain
- ❖ Excessive sympathetic outflow, or elevated peripheral catecholamine levels

- Stress/PTSD
- Anxiety
- Loss of attraction to partner
- Relationship difficulties
- Psychosis
- Depression

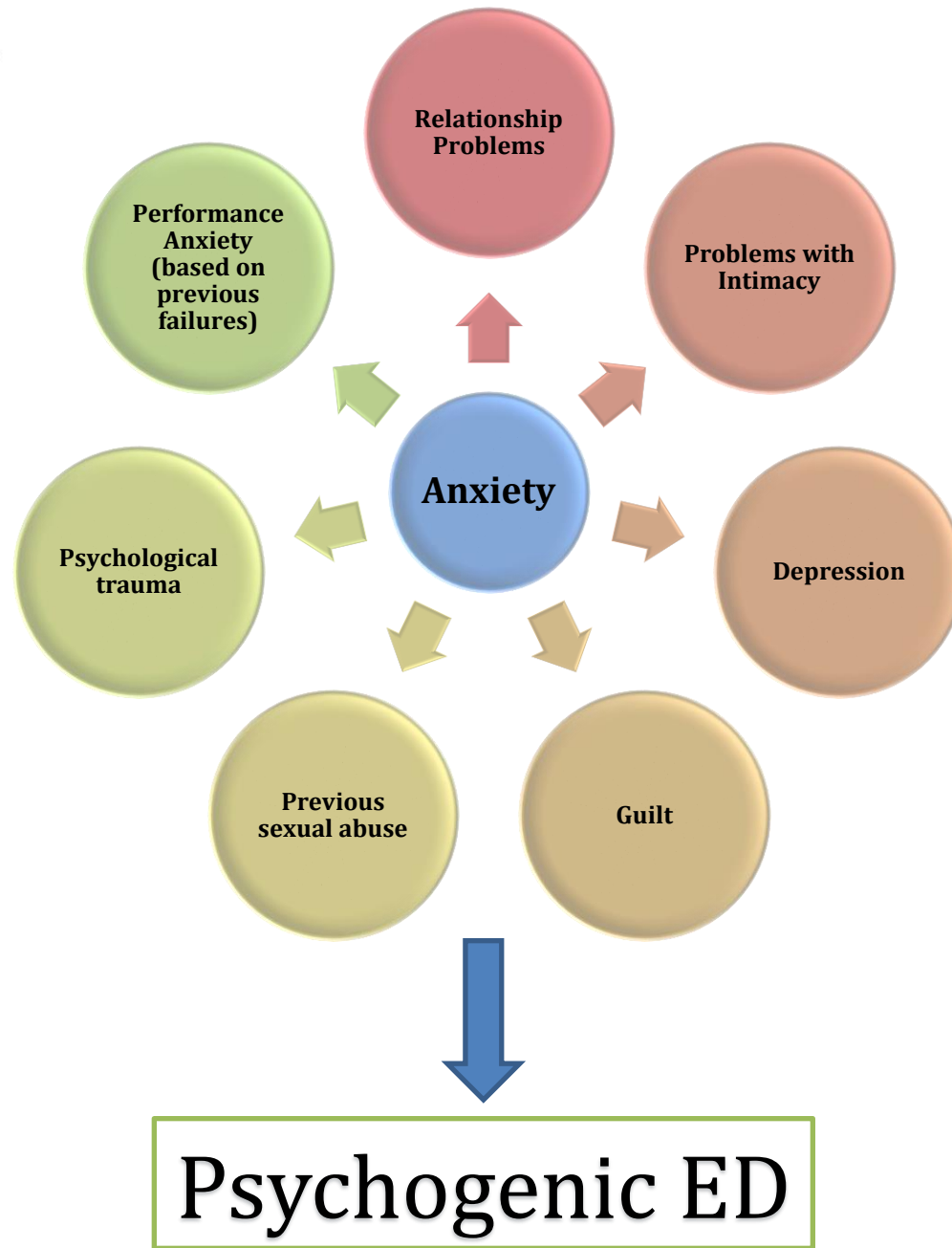
Clues differentiating psychogenic from organic causes

- Psychogenic
 - Sudden onset
 - Situational
 - Normal spontaneous erections (nocturnal & EMT)
 - Normal erection with masturbation
 - Relationship problems
 - Significant life event
 - Anxiety, depression, fear
- Organic
 - Gradual onset
 - All situations
 - Reduced or absent spontaneous erections (nocturnal & EMT)
 - No erections with masturbation
 - Penile pain



Relationship Difficulties

- Current relationship status
- Length of relationship
- Previous sexual partners and relationships
- Partner issues e.g. painful intercourse/menopause/long-term illness



Prevalence (literature)

- 52% of men have ED (40-70 years of age)
- 8% of 40 year old men; 40% of 60 year old men
- Estimate in UK is 2.3 million
- Worldwide prevalence of erectile dysfunction around 177 million cases
- has been predicted to double (and reach 322 million cases by the year 2025).
- De Berardis, et al. (2005) decreased QoL in men with Type 2 DM
- ED can be the first presentation of cardiovascular disease. The average time between onset of ED and 1st cardiac event is 3 ½ years

What does this mean for practice?

- Incidence of ED is >1:10
- On average, it takes 3.5 - 6.6 years for patients to seek advice
- On average, relationships change within 6 months of a sexual dysfunction
- Patients do not know the words to use to ask for help
- Evident silence in discussing sexual problems
- Little or no advertising of Men's health - is it an agenda item?
- Patients are devastated by ED (or the implications of ED)



Risk Factors for ED

- General health status
- Diabetes mellitus
- Cardiovascular disease
- Concurrence of other GU diseases
- Psychiatric or psychological disorders
- Chronic diseases
- Smoking
- Medications
- Hormonal factors also serve as well-defined risk factor-associated conditions



Endocrine causes of ED

- Antiandrogen therapy
- Pituitary Abnormalities
- Hyperthyroidism
- Hyperprolactinaemia
- Hypogonadism
 - Raised SHBG
 - Raised Prolactin
 - Low testosterone

If two consecutive testosterone results are 12nmol/L or less (provided blood taken between 09.00 and 11.00):



Endocrine opinion

Drugs associated with ED

- Antihypertensives
 - β blockers
 - Thiazides
 - Centrally acting drugs
- Antidepressants
 - Tricyclics
 - MAO inhibitors
 - SSRIs
- Anticholinergics
 - Atropine
- Antipsychotics
 - Phenothiazines
- Anxiolytics
 - Benzodiazepines
- Psychotropic drugs
 - Alcohol
 - Opiates
 - MDMA/Amphetamines
 - Cocaine
 - Tobacco



ED and Coronary Artery Disease

- Generalised atherosclerosis
- Penile arteries smaller than coronary arteries
- ED pre-dates coronary artery disease
- Man with ED and no cardiac symptoms is a cardiac patient until proven otherwise
- Increased peripheral vascular resistance
- Enhanced basal and myogenic tone has been observed in arteries



Arteriogenic Cause of ED

- Reduced arterial perfusion, increased peripheral vascular resistance & enhanced basal and myogenic tone may collectively contribute
- Common risk factors
 - IHD/Hypertension
 - Smoking
 - Diabetes
 - Hyperlipidaemia
 - Peripheral vascular disease
 - Blunt perineal or pelvic trauma – leading to focal stenosis
 - Pelvic irradiation
- Long-distance cycling is also a risk factor – causes vasculogenic and neurogenic changes



Cavernous (Venogenic)

- **Degenerative changes** (aging, Peyronie's disease and diabetes) or traumatic injury to the tunica albuginea (e.g. penile fracture) - impairs the compression of the subtunical and emissary veins.
- **Loss of elasticity of the penile sinusoids** associated with increase in collagen deposition & reduction in fibre elasticity - may be seen in diabetes, hypercholesterolaemia, vascular disease, penile injury, or aging.
- **Veno-occlusive dysfunction** may result from a variety of pathophysiologic processes: degenerative changes to tunica, fibroelastic structural changes, insufficient relaxation of trabeculae, and venous shunting (venous leak).



Neurogenic causes of ED

- Any central lesions of brain, especially MPOA, PVN, hippocampus - these are important integration centres
- Spinal trauma - nature, location, and extent of injury largely determines EF
- Pelvic surgery/radiotherapy → Neuropraxia
- Myelodysplasia (spina bifida)
- Multiple sclerosis
- Intervertebral disc lesion
- Peripheral neuropathies
 - Inherited neuropathies
 - Diabetic neuropathy
 - Alcohol
 - HIV



What to assess?

- Is it erection trouble or premature ejaculation?
- How long has there been a problem
- What precipitated it? (if known)
- Do you get erections in the morning/night-time
- Are you still intimate with your partner
- Can you penetrate?
- What treatment have you tried?
- Correct treatment/dosing?

Hypertension

- Hypertension is an independent risk factor for ED
- Cardiovascular complications such as ischemic heart disease and renal failure are associated with even higher ED prevalence
- ED may be compounded by treatments given to manage hypertension (nitrates, beta blockers, etc.) & some treatments may be an absolute contraindication (e.g. patients taking nitrates)





Diabetes Mellitus

- Common chronic disease, affecting 0.5% to 2% worldwide
- In 12% of diabetic men, deterioration of sexual function can be the first symptom
- Prevalence of ED is three times higher in diabetic men (28% versus 9.6%)
- Causes vascular and neurogenic changes



Chronic Renal Failure

- Erectile dysfunction can be seen in up to 40–80% of haemodialysis patients.
- ED in CKD is multifactorial - includes decreased arterial blood flow, venous leakage, altered penile smooth muscle function, hormonal disturbances, side effect of medications and neurogenic changes.
- Uremia decreases NO bioavailability



History

- Medical/Surgical/Mental Health
- Medication
- Smoking
- Alcohol
- Recreational drug use



History (continued)

- Detailed description of problem, is it ED?
- Causative factors
- Sexual desire/libido
- Ejaculatory disorders
- Impact on quality of life and on relationship
- Expectations of treatment

And finally.....

- Sexual activity demands energy
- Approximately 3-5 METs are needed for 'normal' sex
- Equates to mowing a small lawn or climbing 2 flights of stairs
- If you cannot do either, you are not fit enough for sexual activity

Summary

- ED is very common
- Identify it early & any potential risk factors – makes treatment 'easier'
- Ask – no-one else will
- Aggressive management (where possible) to regain sexual self confidence & prevent neuropraxia
- May herald future major cardiac/cerebrovascular event – seek onward referral, advice & intervention